

Polycystic Ovary Syndrome: A Review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in premenopausal women. Heterogeneous by its nature, PCOS is defined as combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses. The etiology of the syndrome remains unknown, but evidence suggests that PCOS might be a complex multigenic disorder with strong epigenetic and environmental influences, including diet and lifestyle factors. It affects 8% to 13% of reproductive-aged women. Polycystic ovary syndrome (PCOS) is associated with hormonal, biochemical disturbance and adverse cosmetic, reproductive, metabolic, and psychological consequences, resulting in reduced health-related quality of life (HRQoL). The most recent international guidelines set lifestyle management as the cornerstone of the PCOS treatment.

KEYWORDS: *Polycystic ovary syndrome, Lifestyle management, Health related quality of life, ovarian dysfunction*

INTRODUCTION

A number of illnesses are gender-specific. Gynecological issues involve the disability in reproductive or the estrogen-controlled organs in the females. While a few of these feminine problems are curable, some may be chronic, or even fatal. Many of these disorders interfere with fertility. With the upsurge in the invasion of, and exposure to chemicals or synthetics, which are to large extent endocrine disruptors, the instances of hormonal disturbances in females are on a sharp rise. One of these commonly encountered reproductive and hormonal irregularities includes POLYCYSTIC OVARY SYNDROME. (Patel et al. 2018) Polycystic Ovarian Syndrome (PCOS) also referred to as hyperandrogenic an ovulation (HA), or Stein-Leventhal syndrome (Evans and Riley, 1958), is the commonest endocrine disorder that affect women in their reproductive age. (Azziz et al, 2016) Polycystic ovary syndrome (PCOS) is a disorder that is characterized by a combination of signs and symptoms such as: androgen excess (hirsutism and/or hyperandrogenaemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology (PCOM an excessive number of parental follicles in the ovaries). (Escobar-Morreale, 2018) PCOS is heterogenous in its presentation in pre menopausal women. (Huhtaniemi, 2018) Symptoms of PCOS emerge during the early pubertal years affecting upto 15%–20% of women at reproductive age. (Moghadam et al. 2018) Women with PCOS may complain about irregular menstrual periods and/or heavy menstrual bleeding, infertility, excessive growth of facial and body hair, obesity, seborrhoea, and cystic skin breakout. The effect of these indications on a woman's quality of life may be profound and can result in psychological distress. (Cronin et al. 1998) Pathophysiology of this heterogeneous disease has

not been clearly determined, yet it is accepted that it results from genetic, metabolic, and environmental factors. (Moghadam et al. 2018) PCOS is associated with adverse clinical complications including, reproductive (complications or infertility), metabolic (expanded danger of increased glucose resistance, type 2 diabetes and cardiovascular illness) and mental (increased anxiety and depression) disturbances. All these factors are responsible in decreasing quality of life of a women suffering with PCOS. (Moran et al. 2019) Various environmental factors contribute in the occurrence and treatment of this syndrome, among which dietary pattern, physical activity, smoking and stress could be highlighted. (Faghfoori et al. 2017)

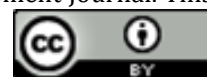
Management of both those in danger for PCOS and those with a confirmed PCOS diagnosis includes proper education, healthy lifestyle interventions including diet and exercise, and therapeutic interventions targeting their symptoms. (Witchel et al. 2019) Exercise training has reliably appeared to improve menstrual regularity, cardio respiratory fitness, self-esteem and HRQOL while decreasing insulin resistance and body fat.^[10] The international clinical practice guidelines for PCOS emphasize diet and exercise as first line management of clinical signs and symptoms of this syndrome.^[11] The therapy of PCOS is typically centered on improving its symptoms. Effective treatment can reduce the burden of these symptoms as well as the associated psychological stress and therefore improve health-related quality of life (HRQL). (Cronin et al. 1998) (Kazemi et al, 2020) The exact PCOS a etiology is unknown, but increased adiposity is considered pivotal. Almost 90% of females with PCOS are overweight or obese and even moderate weight loss (e.g., 5%) may result in significant improvement in

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hyperandrogenism and menstrual regularity. (Kite et al. 2019) The primary aim of this study is to determine the effect of diet and exercise in women suffering from Polycystic Ovary Syndrome (PCOS) and check if the stress is reduced in females after recovering.

CHARACTERIZATION OF PCOS:

2.0. The Rotterdam ESHRE/ASRM—Sponsored PCOS Consensus Workshop Group Fertility and Sterility (2003):

Nearness of 2 out of 3 criteria:

1. Polycystic ovaries on ultrasound.
2. Oligovulation or anovulation.
3. Clinical or biochemical indications of hyperandrogenism.

A. Oligovulation or anovulation of PCOS:

When ovulation happens once in a while or erratically, it is oligovulation and as a general rule, is delegated having 8 or less periods in a year. Normally, a woman ovulates or releases a create egg once per month, around halfway through her cycle. (Kazemi et al. 2020)

B. Clinical and biochemical indications of hyperandrogensim:

Clinical or biochemical indication of hyperandrogemism is: hirsutism, acanthuses Nigerians androgenic alopecia, skin break out. Hirsutism: It might be a clinical indication of hyperandrogenism. Hair development is caused on:

- Chin
- Upper lip
- Chest
- Upper back
- Chin
- Lower back
- Upper arm
- Forearm

C. Polycystic ovaries on ultrasound:

Ultrasound is the most extensively used technique for examination of PCOS. The sonographic criteria have been thusly balanced and, along these lines, the addition in ovarian volume (>10 cm³) and the proximity of >12 follicles with a broadness of 2 to 9 mm at smallest in one ovary. In extension to these criteria, other restorative conditions that can cause steady an ovulation and androgen excess should be restricted, for example,

- Hyperprolactinemia/hyperthyroidis
- Congenital adrenal hyperplasia, traditional and no established structure
- Cushing's disorder; secretary ovarian tumor of adrenal androgens

2.1. The Thessaloniki ESHRE/ASRM—Sponsored PCOS (2006):

In 2006, PCOS Society (AE-PCOS) and The Androgen Overabundance disseminated its arranging regarding assurance of polycystic ovary issue. According to this connection, the androgen excess should appear, either by clinical signs, or by biochemical hyperandrogenism.

For diagnosing of the confusion, two of the after criteria would be beneficial:

- polycystic ovaries on ultrasound; and Oligo as well as an ovulation
- Clinical proof of androgen excess

2.2. The Amsterdam ESHRE/ASRM— sponsored third PCOS Consensus, 2012:

Most as of late characterized nearness of 2 out of 3 criteria:

- Hyperandrogenia and additionally hyperandrogenism;
- Menstrual brokenness and additionally polycystic ovary;
- The ultrasound showing up a polycystic ovary. (Patel, 2018)

PATHOPHYSIOLOGY

Pathophysiology of PCOS manages it as a complex infection including uncontrolled ovarian steroidogenesis, over the top oxidative pressure, atypical insulin flagging, and hereditary/natural components. Imperfection in theca cells can somewhat clarify the hyperandrogenemia in patients with PCOS. Ladies with PCOS have theca cells that discharge unnecessary measure of androgens because of an inherent actuation of steroidogenesis even without jungle factors (Nelson et al., 1999). The characteristic dysregulation influences granulosa cells which produce upto multiple times more significant levels of against mullerian chemical in ladies with PCOS in contrast with sound controls (Pellatt et al., 2007; Azziz et al., 2009; Villarroel et al., 2011). Studies show a raised number of follicles, basically pre-antral and little antral follicles, in females with PCOS (Webber et al., 2003). Deformity in apoptotic measures in some developing follicles, in PCOS patients (Das et al., 2008). Then again, diminished insulin affectability owing to a post receptor restricting imperfection in the insulin flagging pathways has been recognized as a natural part of PCOS, free of corpulence (Dunaif, 1997). It was likewise revealed an alterationing eneexpression of certain major parts in insulin flagging pathways by microarray quality examination (Cortón et al., 2007, 2008). Additionally, PCOS has been related with expanded glycol oxidative pressure (González et al., 2006) auxiliary to mitochondrial brokenness (Victor et al., 2009). Oxidative pressure would itself be able to instigate insulin opposition and hyperandrogenism in patients with PCOS (Victor et al., 2009). Familial total of PCOS (Azziz et al., 2004; Chen et al., 2011) and genomic ID of PCOS-vulnerability loci (Chen et al., 2011) support the part of hereditary qualities in the etiology of this illness. A few investigations showed an acquired segment of androgen overabundance in patients with PCOS (Legro et al., 1998; Escobar-Morreale et al., 2005; Yildiz et al., 2006). Moreover, a polymorphic marker in fibrillin 3 quality related with PCOS, D19S884, has been distinguished in free arrangements of families conveying the sickness (Urbanek et al., 2007; Segars and Decherney, 2010).

SYMPTOMS

Anovulation or oligovulation is the commonest symptom of PCOS. Some of the cysts produce androgens, which result in the expression of male-like characters in females. Thus, PCOS leads to appearance of masculine symptoms or 'hyperandrogenism'. Visible signs of hyperandrogenism include weight gain, hirsutism (facial and body hair), abdominal and subcutaneous fat, male-pattern alopecia (hair loss), clitoromegaly (enlargement of the clitoris), deep voice, seborrhea (oily skin), acne etc. Alteration in metabolic profile also occurs. Apart from these morphological features, Insulin resistance is the major symptom of PCOS, it results in hyperinsulinemia, and can lead to diabetes mellitus. High insulin level is responsible for the deposition of fat around the abdomen or central adiposity. In majority of females with PCOS, the body mass index (BMI) is 30 or higher. Co-morbidities of PCOS are hypertension; cardiovascular issues, dyslipidemia, etc. are co-morbidities of PCOS. Women with PCOS are at high risk for the development of early-onset of

cardiovascular disease. The PCOS patients often display delayed healing, sugar cravings, frequent urination, fatigue, blurred vision, mood swing, tingling sensation, anxiety, and depressive episodes. The patients may feel fever, nausea, constipation, vomiting, urinary conditions, etc. Sleep apnea (sleep disorder in which breathing repeatedly stops and starts) is another symptom of PCOS, arising due to altered sex steroid level.

PCOS can put a female at the danger for uterine disease, as the overall high estradiol level and the absence of progesterone because of ovarian glitch builds the danger of endometrial hyperplasia. Bodily fluid lacking endocervix, and smooth vagina is a component of PCOS, which can be seen during a pelvic test. Because of the hormonal awkwardness in PCOS, skin grows light earthy colored or dark fixes, a condition known as 'acanthosis nigricans'. Skin of neck, armpits, thighs, and bosoms are more inclined to this skin pigmentation. Likewise, skin labels show up in those districts. Indeed, the dim pigmentation is a cutaneous marker for insulin opposition. The metabolic disorder resultant of PCOS is huge. Truth be told, the pathologies are reciprocal, as metabolic condition, and the steady irritations, can prompt PCOS. In light of confirmations, the connection between non-alcoholic greasy liver sickness (NAFLD), a constant liver infection portrayed by hepatic harm from greasy liver penetration prompting end-stage liver illness, and PCOS has been followed, which has demonstrated a novel hepatoovarian pivot. Notwithstanding, PCOS indications can be considered as a range, as the signs fluctuate among races, and people. Hirsutism is gentle or missing in PCOS females of South Asian and Scandinavian source, for the androgen affectability of pilo-sebaceous organs vary, however Middle Eastern and Mediterranean beginning PCOS patients are more influenced by hirsutism. Ovarian hyper stimulation disorder (OHSS) is a state of liquid assortment in the mid-region and chest (ascites and pleural radiation), coming about because of inconveniences in ovulation acceptance. This shift of liquids into the third space for example stomach and pleural depression is because of vascular hyper permeability. OHSS is evaluated dependent on the manifestations. It very well may be gentle, prompting weight acquire, stomach agony, sickness and heaving swelled mid-region because of ovarian distension (from 5 to 12 cm), low urinary sodium discharge, oliguria and so forth. Be that as it may, in some cases, the condition is extreme, showing in trouble with breathing; ionic irregularity; profound vein apoplexy; hypovolemia, crack of a pimple in an ovary prompting genuine dying; ovarian twist; pregnancy misfortune from unsuccessful labor, or end in view of entanglements; aspiratory embolism, kidney disappointment and so on. Ovarian twist is a health related crisis, and it can remove blood to the ovaries, causing serious agony and dying. In genuine cases, passing can happen because of hypovolemia, hyper coagulation, respiratory, and circulatory breakdown. It implies the sodium, and potassium siphon usefulness is influenced. The chemical HCG (human chorionic gonadotrophin) makes the ovary go through broad luteinization, causing the arrival of overabundance estrogens, progesterone, and nearby cytokines. Vascular endothelial development factor (VEGF) is a substance that initiates vascular hyper permeability. VEGF initiates HCG to build slender penetrability in OHSS. PCOS makes the female powerless to OHSS. Aside from the actual impacts, PCOS can influence the mental parts of a patient's life. Tension, despondency, gorging jumble, and bipolar problem have

been seen as PCOS co-morbidities. In postmenopausal ladies with PCOS, cerebral white matter creates injuries. The neural pathology is probably going to be because of neural harms. (Patel et al, 2018)

ETIOLOGY/CAUSE:

The exact reason for PCOS is dark; it is gotten on to be a multi factorial condition with a genetic part. Around 20–40% of first-degree female relatives of women with PCOS proceed to make PCOS themselves, contrasted with evaluated 4–6% prevalence inside the normal people. The fundamental driver of PCOS:

- Increased androgen level
- Life style
- Environments
- Increased insulin
- Increased estrogen
- Genetic inclination
- Weakened resistant framework
- Irregular periods
- Evaluation and Diagnosis
- Hormonal disturbances
- Dirty nourishment
- Inflammation (Morang et al. 2019)

TREATMENT OF ADOLESCENT PCOS

Young people giving PCOS highlights, before the conclusion is affirmed, frequently require the board of their side effects. The administration of youths with an unmistakable analysis of PCOS ought to incorporate education about the condition and lifestyle modifications. The interventions can be individualized to focus on the first grumbings and manifestations. Interventions incorporate metformin, joined oral preventative pills (COCPs), spironolactone, and other medicines for hirsutism and skin break out. The executives ought to likewise incorporate management of comorbidities, regular follow up, and an arrangement for change to grown-up care suppliers.

A. Education and Counseling

Education and counseling about the condition is extremely important. The reason and discussion of PCOS ought to be culturally sensitive moreover as acceptable, comprehensive, and tailored to the individual. This discussion ought to improve empathetic approach, promote self-care, and highlight peer support groups, which are available in multiple countries. Healthy lifestyle interventions are to be incorporated in management of adolescents with PCOS because as a large proportion of all adolescents are obese/overweight or are at high risk of gaining extra weight. Lifestyle interventions include multiple components, including physical activity, healthy diets, decreased sedentary behaviors, and behavioral strategies. Adherence to these lifestyle interventions can be improved by management of psychological factors such as disordered eating, anxiety, body image concerns, which are common in adolescents. Lifestyle interventions in PCOS women have shown improvements in their quality of life.

Limited data is available regarding dietary changes to achieve weight loss in PCOS. A hypo caloric diet (40 g of fat per day) and low-carbohydrate diet (20 to 40 g/d) during 12 weeks may improve weight and menstrual irregularities with no difference between the diets. According to a study, low-glycolic load and low-fat diet during 6 months period helps in weight reduction with no difference between diets. Nutrition education to PCOS women with exercise training

and behavioral therapy for 12 months results in weight loss, and also in improvement of menstrual irregularities as well as androgen levels. Results in better maintenance of health can be maintained by physical activity of longer duration, frequency, and intensity. Mild to moderate/ vigorous physical activity for a time period at least 60 minutes per day is associated with improved physical and psychosocial health in children and adolescents. Activities such as watching television and the use of tablets, computers, and/or mobile phones to 2 h/d are to be limited in adolescents and relates to better health.

B. Metformin

Metformin is the absolute most examined insulin sensitizer in PCOS. It is usually utilized in youths 15 to 19 years old in spite of being "off mark" for this sign. Moreover, as indicated by the new global proof based rules for evaluation and the executives of PCOS, "The utilization of metformin notwithstanding way of life could be considered in young people with a reasonable finding of PCOS or with side effects of PCOS before the analysis is made". A meta-investigation of metformin use with and without way of life changes in PCOS (counting two RCTs in teenagers showed helpful impacts on BMI and monthly cycles. There have been various observational examinations and six RCTs assessing the impact of metformin on an aggregate of 275 young people with PCOS. These examinations have shown transient helpful impacts for the most part in young people with overweight/heftiness. Metformin portions utilized went from 1000 to 2000 mg every day with the significant result being gentle gastrointestinal pain. Impediments are that the recurrence of results and adherence to prescriptions has not been completely detailed. Results can be diminished by beginning metformin at a lower portion with moderate additions and the utilization of broadened discharge arrangements. RCTs were mostly of half year span; just one examination kept going two years, and no more drawn out term contemplations have been accounted for. Metformin at a portion of 1700 to 2000 mg/d is related with more prominent improvement of BMI, and COCPs are related with progress in feminine inconsistency and skin break out as indicated by a meta-examination of metformin versus oral contraceptives in young people with PCOS and including four RCTs (170 teenagers). Both metformin and oral contraceptives had comparable helpful consequences for hirsutism, fatty substances, and high-thickness lipoprotein cholesterol; however the appraisals of impact were gotten from bad quality proof including little investigations. Meta-investigations remembering bigger number of RCTs for ladies with PCOS showed restricted or no advantage of insulin sensitizers on hirsutism. Metformin additionally can be utilized notwithstanding COCPs, particularly in youths with PCOS and BMI ≥ 25 kg/m², just as high-metabolic danger gatherings like certain nationalities and people at expanded danger of type 2 diabetes.

C. COCPs

COCPs (estrogen and progestin preparations) should be considered for management of menstrual irregularity and/or clinical hyperandrogenism in adolescents with a clear diagnosis of PCOS and in adolescents at risk of PCOS before the diagnosis is confirmed according to the recent international evidence-based guidelines. There are limited evidence-based data regarding specific types or doses of progestins, estrogens, or combinations of COCPs for management of PCOS in adolescents and women, but the

lowest effective estrogen dose (20 to 30 mg of ethinylestradiol) should be considered. Contraindications such as thromboembolism risk should be assessed when prescribing COCPs by obtaining thorough medical histories of the patient and her family. In most instances, 35 mg of ethinylestradiol plus cyproterone acetate preparations should not be considered first line in PCOS. Duration of treatment has not been evaluated beyond 24 months in adolescents with PCOS. However, COCPs have been used for contraception in longer periods of time. COCPs improve menstrual irregularity in adolescents with PCOS. COCPs should be also offered when contraception is required and/or medical treatment of hirsutism or acne is needed. When no contraception is required, menstrual irregularity alone can also be managed with cyclical medroxyprogesterone acetate (10 mg per day for 10 days). This can be offered when there is a desire to have fewer menstrual cycles and/or a preference for not taking daily medications or being on COCPs due to cultural reasons.

D. Management of Acne

Treatment will be based upon severity of acne with following goals: suppression of *Propionibacterium acnes*, reduction of sebum production, prevention of formation of microcomedones, and reduction of inflammation to prevent scarring. Mild acne can be managed initially with topical retinoids or over-the-counter topical treatments such as benzoyl peroxide 0.1%/ 2.5% (Epiduo gel) or the combination of the two agents as well as appropriate skin care. Moderate and severe cases of acne require an absolute need of addition of systemic antibiotics (macrolides) for 3 or 4 months. These can be used in management of moderate to severe acne in adolescents. Regular appointments with dermatologist should be considered when the response is poor in severe cases, as acne might have major negative impact on adolescent psychosocial well-being.

SUMMARY

PCOS is a complex disorder with onset during the early pubertal years. At this time, an individualized treatment plan can be developed for the adolescent girl with features of PCOS. Attention to the history, physical examination, and laboratory data is important to identify adolescent girls at risk to develop PCOS. Whereas deferring diagnostic labeling may be appropriate, treatment of clinical features and comorbidities is vital to the health and self-esteem of these patients. One future goal includes prevention through timely identification of at-risk prepubertal and early pubertal girls through lifestyle interventions.

The rundown of elements associated with the pathophysiology keeps on extending, with accumulating proof showing that hyperandrogenism is a crucial factor influencing numerous tissues. GWASs have distinguished qualities basic to both Han Chinese and white populaces that are engaged with neuroendocrine, metabolic, and conceptive pathways. Information acquired from creature models has reliably involved testosterone as a significant factor in the pathogenesis of PCOS. The significant commitments of ectopic fat stockpiling and adipocyte androgen biosynthesis are arising. Promising clinical and preclinical information highlight neuroendocrine inclusion with supporting parts for GABA flagging and neuronal ARs.

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